RESPONSE

I. Status of the Claims

No claims have been amended. No new claims have been added. Claims 1-12 are presently pending in the case.

II. Rejection of Claims Under 35 U.S.C. § 101

The Action rejects claims 1-12 under 35 U.S.C. § 101, as allegedly lacking a patentable utility. Applicants respectfully traverse.

Applicants respectfully submit that the question of utility is a straightforward one as established by the courts. As set forth by the Federal Circuit, "(t)he threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999) (citing *Brenner v. Manson*, 383 U.S. 519, 534 (1966)). Additionally, the Federal Circuit has stated that "(t)o violate § 101 the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992), emphasis added. *Cross v. Iizuka* (224 USPQ 739 (Fed. Cir. 1985); "*Cross*") states "any utility of the claimed compounds is sufficient to satisfy 35 U.S.C. § 101". *Cross* at 748, emphasis added. Indeed, the Federal Circuit recently emphatically confirmed that "anything under the sun that is made by man" is patentable *(State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 47 USPQ2d 1596, 1600 (Fed. Cir. 1998), citing the U.S. Supreme Court's decision in *Diamond vs. Chakrabarty*, 206 USPQ 193 (S.Ct. 1980)).

The legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. According to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 Federal Register 1098, January 5, 2001).

In *In re Brana,* (34 USPQ2d 1436 (Fed. Cir. 1995), "*Brana*"), the Federal Circuit admonished the P.T.O. for confusing "the requirements under the law for obtaining a patent with the

requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago.

Brana at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections under 35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between 35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted. In assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (C.C.P.A. 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Even under the newly installed utility guidelines, Applicants note that MPEP 2107 (II)(B)(1) states:

(1) If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility. (MPEP 2107 (II)(B)(1))

Applicants assert that SEQ ID NO:1 (and fragments presented in SEQ ID NOS:3 and 5) encodes a novel human channel protein. This assertion is supported by clear evidence that those skilled in the art at the time the present application was filed knew that APX was an apical plasma membrane protein that plays a role in the functional expression of the amiloride-sensitive epithelial sodium channel in *Xenopus laevis* (Staub O, *et al.*, 1992, J Cell Biol, **119**(6):1497-506: Abstract as **Exhibit A**). Those skilled in the art during the relevant times period also knew that APX functions as a member of a macromolecular complex required for proper epithelial sodium channel function (Zuckerman *et al.*, 1999, J.Biol.Chem. *274*: 23286-23285: Abstract as **Exhibit B**). APX-L (APX-Like) is the human homologue of APX (Schiaffino MV, *et al.*, 1995, Hum Mol Genet: **4**(3):373-82: **Exhibit C**). As explicitly noted in the present specification (on page 2 lines 2-4), the protein encoded by the sequences of the present invention and APXL share a PDZ domain (**Exhibit D**). The present protein contains both an amino-terminus PDZ actin binding domain and carboxy terminal ATP binding and ATPase (V type) motif domains. It is well known that PDZ domains mediate protein-protein interactions and consist of 80 to 90 amino acids comprising six beta-strands (betaA to betaF) and two alpha-helices, A and B, compactly arranged in a globular structure. Peptide binding of the ligand takes place in an elongated surface groove as an antiparallel beta-strand interacts with the betaB strand and the B helix. The PDZ domain allows binding to a free carboxylate group at the end of a peptide through a carboxylate-binding loop between the betaA and betaB strands. PDZ domains are typically present in cytoplasmic proteins where they bind either the carboxyl-terminal sequences of proteins or internal peptide sequences that are involved in forming macromolecular channal complexes like those that have been described for APXL. Thus, Applicants' assertions that the protein of the present invention, like APXL, is indeed a channel protein is fully consistent with the presence of the PDZ domain contained within the protein. Absent any evidence of record that the described PDZ domain somehow fails to function as it does in related proteins, the Examiner has failed to meet his/her burden of establishing that

the Applicants' assertion of protein function is not credible. Accordingly, the Examiner is respectfully requested to either provide data that substantially and specifically refutes the Applicants' asserted function/utility, or withdraw the rejection.

Further, Applicants respectfully submit that the present situation parallels Example 10 of the PTO's Revised Interim Utility Guidelines Training Materials (pages 53-55), which establishes that a rejection under 35 U.S.C. § 101 as allegedly lacking a patentable utility and under 35 U.S.C. § 112, first paragraph as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility, is not proper when there is no reason to doubt the asserted utility of a full length sequence (such as the presently claimed sequence) that has a similarity to a protein having a known function. The function of channel proteins such as that of the present invention is known to those of skill in the art. Thus the rejection of the presently claimed invention under a 35 U.S.C. § 101 and a 35 U.S.C. § 112 first paragraph utility rejection should not have been made and should thus be withdrawn.

Although the above discussion is believed to be dispositive of the utility issue, Applicants would like to further direct the Examiner's attention to the parts of the specification that describe the use of sequences in a gene chip format to provide a high throughput analysis of the relevant cellular "transcriptome", including assessing temporal and tissue specific gene expression patterns, particularly using a high throughput "chip" format (specification at page 4, line 10 through page 12). The Action, however, discounts Applicants' assertions regarding such uses of the presently claimed polynucleotides on DNA chips, perhaps based on the position that such a use would allegedly be generic. As set forth in Applicants' previous Responses, given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described sequences which encode a human channel protein and has been shown to be expressed in human liver, mammary gland, salivary gland, lung carcinoma cells but not the many other human tissue types tested. Thus, Applicants have identified nucleic and amino acid sequences which encode a human channel protein and a characterized tissue expression pattern.

DNA chips clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501 and 6,261,776 (**Exhibits E-J**; copies of issued U.S. Patents not provided pursuant to current United States Patent and Trademark Office policy). Accordingly, the present sequence has a specific utility in such DNA chip applications. Clearly, compositions that enhance the utility of such DNA chips, like the present

sequences, which encode a human channel protein, have identified polymorphisms and a characterized tissue expression pattern, must have utility. The sequences of the present invention which encode a human channel protein and characterized tissue expression patterns provide specific markers for the human genome (see chromosome mapping evidence provided with Applicants' prior response), and that such specific markers are targets for discovering drugs that are associated with human disease. Thus, those skilled in the art would instantly recognize that the present nucleotide sequence would be an ideal, novel candidate for assessing gene expression using, for example, DNA chips, as the specification details. Accordingly, the present sequence has a specific utility in such DNA chip applications. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequence, must also be useful.

The Examiner is further requested to reconsider that, given the huge expense of the drug discovery process, even negative information obtained using these specific markers of expression of a human channel protein with a characterized tissue expression pattern provides very specific markers for the human genome and have great "real world" practical utility. Knowing that a given gene is not expressed in medically relevant tissue provides an informative finding of great value to industry by allowing for the more efficient deployment of expensive drug discovery resources. Such practical considerations are equally applicable to the scientific community in general, in that time and resources are not wasted chasing what are essentially scientific dead-ends (from the perspective of medical relevance). Clearly, compositions that enhance the utility of DNA gene chips, such as the presently claimed sequences encoding a human channel protein, must in themselves be useful. Moreover, the presently described human channel protein provides uniquely specific sequence resources for identifying and quantifying full length transcripts that were encoded by the corresponding human genomic locus. Accordingly, there can be no question that the described sequences provide an exquisitely specific utility for analyzing gene expression. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Finally, while Appellants are well aware of the new Utility Guidelines set forth by the USPTO, Appellants respectfully point out that the current rules and regulations regarding the examination of patent applications is and always has been the patent laws as set forth in 35 U.S.C. and the patent rules as set forth in 37 C.F.R., not the Manual of Patent Examination Procedure or particular guidelines for patent examination set forth by the USPTO. Furthermore, it is the job of the judiciary, not the USPTO,

to interpret these laws and rules. Appellants are unaware of any significant recent changes in either 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit that is in keeping with the new Utility Guidelines set forth by the USPTO. This is underscored by numerous patents that have been issued over the years that claim nucleic acid fragments that do not comply with the new Utility Guidelines. As examples of such issued U.S. Patents, the Board is invited to review U.S. Patent Nos. 5,817,479, 5,654,173, and 5,552,281 (**Exhibits K-M**; each of which claims short polynucleotides; copies of issued U.S. Patents not provided pursuant to current United States Patent and Trademark Office policy), and recently issued U.S. Patent No. 6,340,583 (**Exhibit N**; which includes no working examples; copy of issued U.S. Patent not provided pursuant to current United States Patent and Trademark Office policy), none of which contain examples of the "real-world" utilities that the Examiner seems to be requiring. As issued U.S. Patents are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph (see Section VIII(B), below), Appellants submit that the present polynucleotides must also meet the requirements of 35 U.S.C. § 101. While Appellants understand that each application is examined on its own merits, Appellants are unaware of any changes to 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit, since the issuance of these patents that render the subject matter claimed in these patents, which is similar to the subject matter in question in the present application, as suddenly non-statutory or failing to meet the requirements of 35 U.S.C. § 101. Thus, holding Appellants to a different standard of utility would be arbitrary and capricious, and, like other clear violations of due process, cannot stand.

For the reasons described above, the present invention clearly has specific, substantial, credible and well established utility. Therefore, Applicants submit that the rejection of claims 1-12 under 35 U.S.C. § 101 has been overcome and the Examiner is respectfully requested to withdraw the pending rejection of claims 1-12 under 35 U.S.C. § 101.

III. Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

The Action rejects claims 1-12 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by a specific, substantial, and credible utility or a well-established utility. Applicants respectfully traverse.

Applicants submit that as claims 1-12 have been shown to have "a specific, substantial, and credible utility", as detailed in section II above, the present rejection of claims 1-12 under 35 U.S.C. § 112, first paragraph, cannot stand.

Applicants therefore request that the rejection of claims 1-12 under 35 U.S.C. § 112, first paragraph, be withdrawn.

IV. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Myers have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

February 20, 2004
Date

Peter G Setterquist Reg No 40162

Lance K. Ishimoto Reg. No. 41,866
Attorney for Applicants

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EXHIBIT A

J Cell Biol. 1992 Dec;119(6):1497-506.

Related Articles, Links

Primary structure of an apical protein from Xenopus laevis that participates in amiloride-sensitive sodium channel activity.

Staub O, Verrey F, Kleyman TR, Benos DJ, Rossier BC, Kraehenbuhl JP.

Swiss Institute for Experimental Cancer Research, University of Lausanne, Epalinges.

High resistance epithelia express on their apical side an amiloride-sensitive sodium channel that controls sodium reabsorption. A cDNA was found to encode a 1,420-amino acid long polypeptide with no signal sequence, a putative transmembrane segment, and three predicted amphipathic alpha helices. A corresponding 5.2-kb mRNA was detected in Xenopus laevis kidney, intestine, and oocytes, with weak expression in stomach and eyes. An antibody directed against a fusion protein containing a COOH-terminus segment of the protein and an antiidiotypic antibody known to recognize the amiloride binding site of the epithelial sodium channel (Kleyman, T. R., J.-P. Kraehenbuhl, and S. A. Ernst. 1991. J. Biol. Chem. 266:3907-3915) immunoprecipitated a similar protein complex from [35S]methionine-labeled and from apically radioiodinated Xenopus laevis kidney-derived A6 cells. A single integral of 130-kD protein was recovered from samples reduced with DTT. The antibody also cross-reacted by ELISA with the putative amiloride-sensitive sodium channel isolated from A6 cells (Benos, D. J., G. Saccomani, and S. Sariban-Sohraby. 1987. J. Biol. Chem. 262:10613-10618). Although the protein is translated, cRNA injected into oocytes did not reconstitute amiloride-sensitive sodium transport, while antisense RNA or antisense oligodeoxynucleotides specific for two distinct sequences of the cloned cDNA inhibited amiloride-sensitive sodium current induced by injection of A6 cell mRNA. We propose that the cDNA encodes an apical plasma membrane protein that plays a role in the functional expression of the amiloride-sensitive epithelial sodium channel. It may represent a subunit of the Xenopus laevis sodium channel or a regulatory protein essential for sodium channel function.

PMID: 1334959 [PubMed - indexed for MEDLINE]

: J Biol Chem. 1999 Aug 13;274(33):23286-95.

Related Articles, Links

Association of the epithelial sodium channel with Apx and alpha-spectrin in A6 renal epithelial cells.

Zuckerman JB, Chen X, Jacobs JD, Hu B, Kleyman TR, Smith PR.

Department of Medicine, University of Pennsylvania, Philadelphia, PA, USA.

Recent molecular cloning of the epithelial sodium channel (ENaC) provides the opportunity to identify ENaC-associated proteins that function in regulating its cell surface expression and activity. We have examined whether ENaC is associated with Apx (apical protein Xenopus) and the spectrin-based membrane cytoskeleton in Xenopus A6 renal epithelial cells. We have also addressed whether Apx is required for the expression of amiloride-sensitive Na(+) currents by cloned ENaC. Sucrose density gradient centrifugation of A6 cell detergent extracts showed co-sedimentation of xENaC, alpha-spectrin, and Apx. Immunoblot analysis of proteins co-immunoprecipitating under high stringency conditions from peak Xenopus ENaC/Apx-containing gradient fractions indicate that ENaC, Apx, and alpha-spectrin are associated in a macromolecular complex. To examine whether Apx is required for the functional expression of ENaC, alphabetagamma mENaC cRNAs were coinjected into Xenopus oocytes with Apx sense or antisense oligodeoxynucleotides. The two-electrode voltage clamp technique showed there was a marked reduction in amiloride-sensitive current in oocytes coinjected with antisense oligonucleotides when to compared with oocytes coinjected with sense oligonucleotides. These studies indicate that ENaC is associated in a macromolecular complex with Apx and alpha-spectrin in A6 cells and suggest that Apx is required for the functional expression of ENaC in Xenopus epithelia.

PMID: 10438504 [PubMed - indexed for MEDLINE]

1: Hum Mol Genet. 1995 Mar;4(3):373-82.

Related Articles, Links

Cloning of a human homologue of the Xenopus laevis APX gene from the ocular albinism type 1 critical region.

Schiaffino MV, Bassi MT, Rugarli EI, Renieri A, Galli L, Ballabio A.

Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX 77030, USA.

Ocular albinism type 1 (OA1) is an X-linked recessive disorder characterized by a major impairment of visual acuity, nystagmus, strabismus, photophobia and retinal hypopigmentation. From the analysis of patients carrying deletions and translocations involving the distal short arm of the X chromosome (Xp22.3) we have identified a region of approximately 110 kb in which the OA1 gene must lie. We have extensively searched for genes in this region using a variety of techniques which included exon amplification, cDNA selection and direct hybridization of cosmid inserts to cDNA libraries. Putative exons identified by exon amplification were used to screen a human retina cDNA library and several cDNA clones corresponding to an approximately 7.5 kb transcript were isolated and characterized. Transcripts of this newly identified gene were found to be abundant in retina and melanoma and could also be detected in brain, placenta, lung, kidney and pancreas. Interestingly, sequence analysis revealed that this new gene encodes a 1616 amino acid protein sharing significant similarities with the Apical Protein from Xenopus laevis (APX) which is implicated in amiloride-sensitive sodium channel activity. The gene, termed APXL (APX-Like), spans approximately 160 kb, contains 10 exons and covers over 70% of the 110 kb critical region for OA1. A truncated pseudogene sharing very high levels of homology with the rat eIF-5 gene, a eukaryotic translation initiation factor, was found to lie in the middle of intron 1. APXL was found deleted in two patients with contiguous gene syndromes including OA1 and in one patient with isolated OA1. Mapping, expression and patient analysis data led us to consider the APXL gene a strong candidate for the OA1 gene. DNA from 57 unrelated patients with OA1 was, therefore, scanned for mutations in the coding region, using both SSCP analysis and direct sequencing. No functionally significant mutation was identified, suggesting that APXL is not directly involved in OA1. Further studies are needed to clarify the physiologic role of this highly conserved gene.

PMID: 7795590 [PubMed - indexed for MEDLINE]

☐ 1: NP_001640. apical protein of...[gi:4502175]

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  TITLE     Cloning of a human homologue of the Xenopus laevis APX gene from
            the ocular albinism type 1 critical region
  JOURNAL   Hum. Mol. Genet. 4 (3), 373-382 (1995)
  PUBMED    7795590
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NCBI

NCBI Conserved Domain Summary

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(1616 letters)

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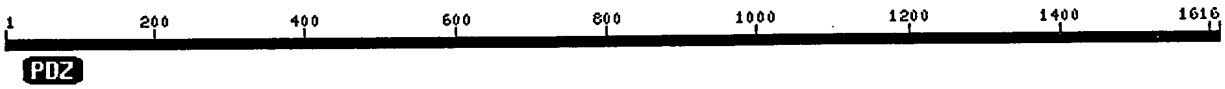
Click on boxes for multiple alignments



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